

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
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PDUFA Goal Date	August 18, 2021
OSE RCM #	2020-1527
Reviewer Name(s)	Theresa Ng, Pharm.D., BCPS
Team Leader	Laura Zendel, Pharm.D., BCPS
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	August 04, 2021
Subject	Evaluation of Need for a REMS
Established Name	Avalglucosidase alfa
Trade Name	Nexviazyme
Name of Applicant	Gemzyme Corporation (Gemzyme)
Therapeutic Class	Recombinant human acid α -glucosidase (rhGAA)
Formulation(s)	100 mg/vial (reconstituted at 10 mg/ml) Injection, lyophilized powder for reconstitution for intravenous infusion
Dosing Regimen	Two dosing regimens based on the intended patient population: <ul style="list-style-type: none">Patients with Late-Onset Pompe Disease (LOPD): 20 mg/kg BW admin every other week <div style="background-color: #cccccc; height: 40px; width: 100%; margin-top: 10px;"></div>

(b) (4)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nexviazyme (avalglucosidase alfa) is necessary to ensure the benefits outweigh its risks. Genzyme Corporation (Genzyme) submitted a Biologics Licensing Application (BLA) 761194 for Nexviazyme with the proposed indication for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (PD). The risks associated with Nexviazyme include hypersensitivity reactions including anaphylaxis and infusion-associated reactions (IARs). The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Rare Diseases and Medical Genetics (DRDMG) agree that a REMS is not needed to ensure the benefits of Nexviazyme outweigh its risks. Hypersensitivity reactions including anaphylaxis and IARs are known class effects of other enzyme replacement therapy (ERT) approved in the United States (US) for the treatment of PD. The risks associated with Nexviazyme are comparable and not clinically different to currently approved ERT for the same indication. Labeling consisting of a Boxed Warning (BW) and Warnings and Precautions statements for hypersensitivity reactions, including anaphylaxis and IARs, will be used to communicate these risks and is consistent with labeling for similar products.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nexviazyme (avalglucosidase alfa) is necessary to ensure the benefits outweigh its risks. Genzyme Corporation (Genzyme) submitted a Biologic Licensing Application (BLA) 761194 for Nexviazyme with the proposed indication for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (PD). This application is under review in the Division of Rare Diseases and Medical Genetics (DRDMG). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Nexviazyme (avalglucosidase alfa also known as neoGAA) is a new molecular entity (NME) proposed as a long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (PD).^a The Applicant proposes avalglucosidase alfa as a second generation recombinant human acid α -glucosidase (rhGAA) consisting of a modified form of alglucosidase alfa with 15-fold increase in mannose-6-phosphate-(M6P) to increase cellular uptake. The Applicant submitted this application as a 351(a) biological license application (BLA).

Nexviazyme is formulated as 100 mg/vial lyophilized powder for reconstitution reconstituted to a concentration of 10 mg/ml for intravenous infusion. The Applicant proposes the following dosing

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

regimen: (1) for patients with Late-Onset Pompe Disease (LOPD) the proposed dose is 20 mg/kg actual body weight (BW) administered intravenously every two weeks, (b) (4)

Avalglucosidase alfa is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761194 relevant to this review:

- 11/19/2013: Avalglucosidase alfa (IND 109569) received Orphan Drug Designation of the modified recombinant human alpha-glucosidase that is conjugated with synthetic bis-manose-6-phosphate-Man6 glycan for treatment of Pompe disease.
- 08/14/2019: The Agency designated fast track status for IND 109569 for avalglucosidase alfa.
- 06/24/2020: The Agency granted Gemzyme's request for a rolling BLA submission in two parts, with the first part comprising of the nonclinical modules and the second part consisting of the remainder of the BLA.
- 07/17/2020: Gemzyme submitted Part 1 of the rolling BLA application which consisted of the nonclinical data.
- 09/18/2020: Gemzyme submitted Part 2 of the rolling BL applicant which consisted of the CMC and clinical data.
- 01/15/2021: Gemzyme submitted 120- day safety update, a corrective package on the data discrepancies of infusion-associated reactions in the integrated Summary of Safety (ISS) and Integrated Summary of Immunogenicity (ISI), and an updated to the labeling proposal.
- 1/26/2021: The Agency issued a mid-cycle communication (MCM) informing the Applicant that there are no major safety concerns identified at this time, and there is currently no plan for a REMS. However, the Agency communicated several concerns to the Applicant. The key points are summarized below:



- The long-term extension treatment periods are still ongoing for each of the trials included in this application and may impact negotiation of the label.
- Additional cases of infusion associated reactions included in the 120 day safety update may impact labeling review.

- 02/26/2021: As communicated in the MCM regarding the efficacy data submitted for the (b) (4) dated January 26, 2021, the Agency issued an information request (IR) for the Applicant to:
 - Provide available pharmacokinetic (PK) and safety data in LOPD patients less than 16 years of age for possible extrapolation approach of efficacy from adult LOPD to pediatric LOPD.
- (b) (4)
- 3/18/2021: The Agency held a Late-Cycle Meeting (LCM) with the Applicant. In the meeting, the (b) (4)
- (b) (4)
- 03/22/2021: The Agency issued an IR to the Applicant as a follow-up to the LCM with the above request for data extrapolation (b) (4)
 - 03/25/2021: The Applicant submitted an amendment with updated population pharmacokinetics (PopPK) to support extrapolation of efficacy from adult patients with LOPD to pediatric patients with LOPD.
 - 04/01/2021: The Applicant submitted further amendments in response to the Agency's IR, dated March 22, 2021.
 - 4/20/2021: The Agency issued a Review Extension- Major Amendment due to the March 25, 2021 amendment submitted by the Applicant which extended the PDUFA date. On the same day, the Agency issued an IR requesting the Applicant to conduct PK simulations and compare exposure across all the age and body weight groups in patients with LOPD and to evaluate alternative dosing regimen in pediatric patients with lower body weight.³
 - 5/3/2021: The Applicant submitted an amendment in response to the Agency's IR, dated 4/20/2021, for PK simulation results conducted with the updated body weight allometric PopPK model built using data from both IOPD and LOPD patients.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Pompe disease (PD), also known as acid maltase deficiency or glycogen storage disease type II (GSD II), is a rare inherited autosomal recessive genetic disease due to mutations in the acid α -glucosidase (GAA) gene resulting in abnormal buildup of glycogen inside cells.⁴ GAA is essential for breaking down lysosomal glycogen to glucose that fuels muscles.^{5,6} This buildup of glycogen results in tissue destruction and impairs the workings of different organs and tissues, especially the heart, respiratory, and skeletal muscles. In the US, PD is estimated to occur at 1 in every 40,000 births.^{7b}

The severity and clinical manifestation of PD depend on the degree of enzyme deficiency. Infantile onset Pompe Disease (IOPD) is the result of complete or near complete deficiency of GAA. In IOPD, symptoms are evident within months of birth, with feeding problems, poor weight gain, muscle weakness, floppiness, and head lag. Respiratory difficulties are often complicated by lung infections and the heart is grossly enlarged. Most babies die from cardiac or respiratory complications before their first birthday. Late onset Pompe disease (LOPD) is the result of a partial deficiency of GAA and may begin anytime from late childhood to adolescence, or even in adulthood.^c The primary symptom of LOPD is muscle weakness progressing to respiratory weakness and death from respiratory failure after a course lasting several years.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Enzyme replacement therapy (ERT) is the only approved treatment for PD. ERT provides an exogenous source of GAA that is taken up into cells and transported into lysosomes where it hydrolyzes glycogen. There are two first generation ERTs consisting of recombinant human acid α -glucosidase (rhGAA) (alglucosidase α) approved for PD: Myozyme (BLA 125141) and Lumizyme (BLA 125291). Lumizyme is the only ERT marketed in the US.

Myozyme received US approval in April 2006 for IOPD based on improved ventilator-free survival in Pompe infants treated with rhGAA enzyme compared to historical, untreated controls.⁸ Lumizyme received approval in May 2010 for LOPD patients greater than 8 years of age who do not have evidence of cardiac hypertrophy. At the time of its approval, the safety and efficacy of Lumizyme had not been demonstrated in IOPD or in LOPD less than eight years of age. The Agency required a REMS with a restricted distribution system called the Lumizyme Alglucosidase Alfa Control and Education (ACE) Program. The goals of the REMS were to mitigate the potential risk of rapid disease progression in IOPD and LOPD patients less than 8 years of age, and to ensure that the known risks of anaphylaxis and severe allergic reactions including the potential risks of severe cutaneous and systemic immune mediated reaction associated with the use of Lumizyme are communicated to patients and prescribers. The Lumizyme ACE Program consisted of a Communication Plan (CP); Elements to Assure Safe Use (ETASU)

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

including prescriber certification (ETASU A) and healthcare facility certification (ETASU C), and documentation of safe use (ETASU D) to ensure patients are counseled and enrolled in the REMS; an implementation system; and a timetable for submission of assessments of the REMS. Based on the physiochemical comparability of Myozyme and Lumizyme, the Agency released the Lumizyme REMS in 2014 with the approval for expanded use of Lumizyme to all ages, including early-onset disease less than 8 years, as the restricted distribution under the ETASU REMS for Lumizyme was no longer necessary.^{9,10} The certification requirement to ensure healthcare facilities appropriately monitor patients was also determined to no longer be necessary as this is a standard procedure for accredited hospitals and infusion center to monitor and treat patients who experience severe allergic reactions including anaphylaxis. Additionally, home infusion agencies also have accreditation standards requiring policies and procedures that address these measures.¹⁰ Furthermore, the REMS assessment results demonstrated completion of the communication plan and achieved acceptable levels in communicating the risks to prescribers and patients.¹¹ Both Myozyme and Lumizyme carry a drug-class boxed warning (BW) for the risk of anaphylaxis, severe allergic reactions, immune-mediated reactions, and the risk of cardiorespiratory failure in patients with compromised cardiac or respiratory function due to infusion-associated reactions.

The standard dosing of alglucosidase alfa is 20 mg/kg of body weight (BW) as an intravenous (IV) infusion every two weeks for both IOPD and LOPD. Although currently approved ERT therapy improves respiratory and functional symptoms, the improvements seen after initial treatment with alglucosidase alfa, however, does not lead to sustained improvement in muscle weakness and impending associated respiratory failure.¹² Therefore, there is an unmet need for additional therapy for PD.

4 Benefit Assessment

The Applicant submitted four studies in support for the efficacy and safety of avalglucosidase alfa: three in patients with LOPD (ETC14028 (COMET), TDR12857 (NEO-1), and LTS13769 (NEO-EXT)), and one in patients with IOPD (ACT114132 (Mini- COMET)). These studies are summarized below.

Avalglucosidase alfa and LOPD:

ETC14028 (COMET), NCT02782741

ETC14028 is the pivotal phase 3 multicenter, multinational, randomized, double-blind comparator-controlled study in treatment-naïve LOPD patients older than 3 years of age. One hundred patients were enrolled and were randomized (1:1) to avalglucosidase alfa (51 subjects) at 20 mg/kg every other week (qow) or alglucosidase alfa (49 subjects) at 20 mg/kg qow for 12 months. The study period is referred to as the primary assessment period (PAP). After the completion of the PAP, the patients continued in an open-label extension treatment period (ETP) where all patients receive avalglucosidase alfa with extension treatment period of 5 years, which is on-going. Randomization was stratified by baseline forced vital capacity (FVC)^d, age,

^d FVC is the amount of air that can be forcibly exhaled from your lungs after taking the deepest breath possible, as measured by spirometry.

sex, and country. The primary endpoint is the change from baseline to 49 weeks in percentage predicted FVC in an upright position. The key secondary endpoint is the total distance (meters) walked during six-minute walk test (6MWT). Other secondary endpoints consist of changes from baseline of inspiratory muscle strength (maximum inspiratory pressure [MIP]), expiratory muscle strength (maximum expiratory pressure [MEP]), lower extremity muscle strength (hand-held dynamometry [HHD]), motor function (Quick Motor Function Test [QMFT]), and health-related quality of life (Short Form-12 [SF-12]). Analysis was conducted on the modified intent-to-treat (mITT) population including randomized patients who received at least one infusion. Non-inferiority (NI) is determined if the lower bound of the two-sided 95% confidence interval (CI) for the Least square (LS) mean difference between the two treatment arms in the primary endpoint is larger than -1.1% (the pre-specified NI margin). Superiority testing is performed only after achieving NI at a two-sided alpha level of 0.05.

The mean age of the study population was 48.1 years, and 94% were White. Treatment arms were balanced for gender. A total of 95 patients completed the study and entered ETP. Five patients in the alglucosidase alfa arm discontinued prematurely during PAP: four for adverse event, and one due to withdrawal of consent. None in the avalglucosidase alfa arm discontinued during PAP.

The clinical reviewer concluded the results showed avalglucosidase alfa was NI to alglucosidase alfa with estimated LS mean change in treatment difference (Week 49) in FVC (% predicted) of 2.4 (95% CI: -0.01 to 5; $p = 0.06$); the lower bound of the 95% CI is larger than NI margin of -1.1%. However, the p -value of 0.06 was higher than the prespecified level of 0.05 and did not meet testing for superiority criteria. Sensitivity analyses accounting for missing data supported the NI conclusion.

For the key secondary endpoint, avalglucosidase alfa was effective in improving distance walked in 6MWT from baseline to week 49 for LOPD patients: LS mean change of 30.0 meter (95% CI: 1.3 to 58.7; $p = 0.04$). No superiority testing was conducted for the 6MWT endpoint as the primary endpoint of % FVC did not meet superiority criteria. For the other secondary endpoints, the estimated treatment differences except MEP favored avalglucosidase alfa arm. Although the changes from baseline numbers for the secondary endpoints trend favorably for avalglucosidase, the differences were not significant.

As of the cutoff date of July 3, 2020, forty-four of the forty-nine patients initially randomized to the alglucosidase alfa arm for the PAP entered the ETP and were switched to avalglucosidase at Week 49. Findings for changes in FVC and 6MWT are summarized below:

- 23 out of the 44 patients had available mean change in FVC from Week 49 to Week 97. The mean change in FVC (% predicted) was -0.1% (95% CI: -3.2, 2.8; $p = 0.92$), which failed to show a statistically significant improvement.
- 26 out of 44 patients had available 6MWT value at Week 97. The mean change in distance walked in 6MWT from Week 49 to Week 97 was 8.6m (95% CI: -20.4 to 37.5; p -value=0.55), which failed to show a statistically significant improvement.

The clinical reviewer determined the data during the ETP do not show any notable improvement in FVC (% predicted) after switch to avalglucosidase alfa at Week 49. Although the 6MWT failed to show statistical significance, the mean changes from Week 49 over time for the switched patients were positive.

TDR12857 (NEO-1), NCT01898364, and LTS13769 (NEO-EXT), NCT02032524

TDR12857 (NEO-1) is a phase 1/2 open label, ascending-dose study of avalglucosidase alfa in both treatment-naïve (Group 1) and previously alglucosidase alfa-treated (Group 2) adult patients with LOPD conducted in seven countries. The primary efficacy endpoint is safety. Twenty-four adult patients with LOPD were enrolled (Group 1, n = 10 and Group 2, n=14). Patients received avalglucosidase at 5, 10, 20 mg/kg qow for 13 doses or 24 weeks. Treatment study lasted for 41 weeks.

LTS13769 (NEO-EXT) is an on-going 6-year open-label extension of study TR12857. The primary endpoints are to assess long-term safety and PK of avalglucosidase alfa. Currently, as of the cut-off date (February 27, 2020), although 19 completed TDR12857, seventeen out of the nineteen LOPD patients enrolled from TDR12857 remained in the extension study; two discontinued due to wish to withdraw and “other.” Patients who initially received lower doses (i.e., 5 or 10 mg/kg qow) of avalglucosidase alfa were switched to 20 mg/kg qow for the remaining duration of the study after providing consent to the switch. Patients on 20 mg/kg continued with this dose. Exploratory efficacy measurements included mean changes from baseline over time in 6MWT distance and FVC (percent predicted).

The mean age at enrollment was 44.8 years for Group 1 and 46.7 years for Group 2. The majority of patients are White (80% for Group 1 and 92.9% for Group 2). Demographics were not well balanced due to limited sample size. The clinical reviewer could not make conclusive determination on the efficacy results of FVC (% predicted) and 6 MWT due to large variations in the standard deviation (SD), though Group 1 results appear to show better performance than Group 2.

Avalglucosidase alfa and IOPD:

ACT14132 (Mini-COMET), NCT03019406

ACT14132 is an ongoing phase 2 multi-stage open-label, ascending-dose, three-cohort study of avalglucosidase alfa in 22 patients under 18 years of age with IOPD, who were previously treated with alglucosidase alfa and showed incomplete treatment response in pre-specified clinical outcomes. Stage 1 includes patients in cohorts 1 and 2 who showed clinical decline in respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis, and Stage 2 included patients in cohort 3 who showed clinical decline in respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis after the highest tolerated dose was determined. The study period lasted 6 months and is referred to as the primary analysis period

(PAP) followed by an open-label extension treatment period (ETP). Patients in cohort 1 (n = 6) received 20mg/kg of avalglucosidase alfa qow, patients in cohort 2 (n = 5) received 40mg/kg of avalglucosidase alfa qow, and patients in cohort 3 (n = 11) were randomized (1:1) to receive 40mg/kg of avalglucosidase alfa qow (n = 5) or alglucosidase alfa at their current stable dose (n = 6). The mean age at enrollment was 6.8 years and the majority of patients were White (54.5%) and Asian (36.4%). Given the limited sample size, baseline demographics were not well-balanced among cohorts and treatment arms. The mean and median ages in the alglucosidase alfa arm within Cohort 3 were younger than those in the other arms. The youngest patient enrolled was over 1 year of age. The primary endpoint of the study was to evaluate the safety profile of avalglucosidase alfa. The key secondary objectives were to characterize the PK profile of avalglucosidase alfa and to evaluate the preliminary efficacy of avalglucosidase alfa compared to alglucosidase alfa for functionality (GMFM-88, QMFT, Pompe-PEDI Functional Skills Scale (Mobility Domain)), echocardiography endpoints, and eyelid position measurements.

For the primary result, with respect to safety, the clinical reviewer concluded no patient required a decrease in dose for safety reasons. The secondary efficacy endpoints were difficult to interpret in this population due to the small number of participants and because the clinical significance of the mean changes between patients treated with avalglucosidase alfa and alglucosidase alfa is unclear. The secondary efficacy results (mean change from baseline to Week 25 of avalglucosidase alfa compared to alglucosidase alfa) are described below:

- Gross Motor Function Measure-88 (GMFM-88) was positive for all cohorts
- Quick Motor Function Test (QMFT) was positive only for cohorts 2 and 3
- Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI) was positive for all cohorts
- Left Ventricular Mass (LVM) Z-score from M-Mode Echocardiograph favored avalglucosidase alfa
- Eyelid Position Measurements favored avalglucosidase alfa at higher dosing

The clinical reviewer concluded that while there were improvements in the numerical values for the secondary endpoints, these values were not statistically significant.

Overall, only the phase 3 pivotal trial, EFC14028, provided adequate efficacy data for avalglucosidase alfa. However, according to the 21 CFR 314.126, substantial evidence of effectiveness can be established with a single adequate and well-controlled clinical investigation supported by confirmatory evidence (CE), which can be derived from the well-established etiology of the disease, the mechanism of action of the therapy, and animal model studies of the disease.

The review team concluded that there was substantial evidence of effectiveness for avalglucosidase alfa in the treatment of Pompe disease based on the EFC14028 trial in those greater than 16 years of age with LOPD. Confirmatory evidence of efficacy is supported based on the well-established etiology of the disease and the mechanism of action of avalglucosidase alfa in nonclinical animal studies in GAAKO

mice, a widely used animal model for Pompe disease, which showed avalglucosidas alfa reduces glycogen levels in tissues and improves muscle functions in mice, consistent with the pathophysiology for Pompe disease.¹³ In addition, avalglucosidase alfa appears to be approximately 3 to 7 fold more potent than alglucosidase alfa in terms of glycogen reduction when compared on a dose basis.

Although pediatric patients less than 16 years old with LOPD were not enrolled in EFC14028, the review team agreed that the natural history and clinical manifestation of Pompe disease in these patients are similar and extrapolation of the efficacy data from adult patients with LOPD to pediatric patients with LOPD is acceptable and justified. Effectiveness in this population were extrapolated from available findings in the clinical development program. In addition, safety data from pediatric patients greater than 12 months of age with IOPD who received a higher dose than used in patients with LOPD and population pharmacokinetic (PK) data in the clinical development program submitted by the Applicant which showed similar PK across all included patients with PD, were leveraged to support approval in pediatric patients with LOPD.

Evidence for efficacy in IOPD was insufficient. The review team noted the small study size of ACT14132 limited assessment of avalglucosidase alfa's effects in this population; the youngest patient enrolled was 12 months of age. No safety data is available for patients below 12 months of age, which was the primary endpoint of the study. As efficacy effects were secondary endpoints and considered exploratory, they do not capture the manifestations of IOPD that have the most impact on survival, such as respiratory failure and cardiac hypertrophy. ACT14132 is not considered as a confirmatory clinical study. In addition, the natural histories and severity of IOPD and LOPD are different, with greater manifestation of cardiac hypertrophy in IOPD compared to LOPD, making extrapolation of the efficacy data from LOPD to IOPD difficult.

5 Risk Assessment & Safe-Use Conditions

The Applicant submitted an Integrated Summary of Safety (ISS) consisting of pooled safety data from the four efficacy studies (ETC14028, TDR12857, LST13769, and ACT14312) in the clinical development program to support the safety of avalglucosidase alfa. The safety population consisted of 138 patients (118 adults and 20 pediatrics) of which 119 LOPD patients were 16 years old and above, and 19 IOPD patients were between 1 to 11 years old. Sixty-one patients were treatment-naïve and 77 were treatment-experienced, having received alglucosidase alfa previously. Three additional IOPD patients were included in the 120-day safety report. There was an imbalance amongst the age groups: there are only 20 pediatric patients in the safety population, and only one pediatric patient (a 16 year old) with LOPD. Of note, no safety data for patients 12 months of age or younger is available.

The most frequently reported adverse reactions (>2%) in the pooled safety population were headache, dizziness, tremor, flushing, hypertension, cough, dyspnea, nausea, diarrhea, vomiting, pruritus, rash, urticaria, rash erythematous, muscle spasm, myalgia, pain in extremity, fatigue, erythema, chest discomfort, pain, and chills. The most frequently reported SAE was pneumonia (3.6%, 5/138). Chills, pyrexia, respiratory distress, respiratory failure, eyelid ptosis all occurred in 2 patients (1%) each. The SAEs in 6 patients were related to hypersensitivity (including anaphylaxis) or infusion associated

reactions (IARs) and will be further described later in section 5.1. The most commonly reported treatment emergent adverse event (TEAE) was nasopharyngitis (30%) and the most common system organ class (SOC) with TEAE was “infections and infestations” (68%). Nine patients who received avalglucosidase alfa discontinued participation during the clinical trials, but only 4 of these patients (3%) did so due to TEAEs (i.e., anaphylaxis [1], IAR [1], non-ST elevation myocardial infarction [1], and pregnancy [1]). These four patients were all treatment-naïve. Five patients withdrew for reasons other than AEs (i.e., enrolled in a gene therapy study [1], withdrew due to the difficulty of visits [1] and other [3]).

Three deaths occurred in the clinical development program. The study investigators concluded the deaths were unrelated to avalglucosidase alfa and the review team agreed with the assessments. One patient met Hy’s Law criteria, however, the review team concluded that the liver injury was associated with the patient’s diagnosis of pancreatic adenocarcinoma and is unrelated to avalglucosidase alfa and the review team did not recommend additional hepatic monitoring with avalglucosidase alfa. The review team also assessed immunogenicity effects with avalglucosidase alfa and concluded it did not have a significant impact on efficacy and safety in the LOPD patients. The immunogenicity impact of anti-drug antibody (ADA) and neutralizing antibody (Nab) in IOPD is unknown as there were no IOPD patients under 12 months old in the clinical development program.

As with ERT drug-class for PD, the potential risks with avalglucosidase alfa treatment include hypersensitivity reactions including anaphylaxis and infusion-associated reactions and are detailed in section 5.1.

5.1 HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS AND INFUSION-ASSOCIATED REACTIONS (IARs)

Among the patients treated with avalglucosidase alfa, 48% (68/141) experienced hypersensitivity reactions such as rash, pruritus, erythema, urticaria, respiratory failure, flushing, blisters, eye swelling, infusion site rash, lip swelling, erythematous rash, allergic rhinitis, asthma, choking, conjunctivitis, contact dermatitis, drug hypersensitivity, eczema, mouth ulceration, respiratory distress, and swollen tongue. Six of these hypersensitivity reactions (12%, 6/68) were severe reactions, consisting of respiratory failure and respiratory distress. Five patients (3 patients from EFC14028 and 2 patients from TDR12857) who received avalglucosidase alfa met Sampson’s criteria for anaphylaxis.^{14,e} The infusion was interrupted, and all five patients were treated with supportive therapies such as antihistamine, steroids, antipyretic, epinephrine, fluids, bronchodilator, and oxygen, alone or in combination.

Forty-two patients (30%) who received avalglucosidase alfa had IARs. The majority of these were mild to moderate in severity. Symptoms consisted of pruritus, rash, headache, urticaria, chills, nausea, erythema, cough, dizziness, fatigue, chest discomfort, diarrhea, hyperhidrosis, influenza like illness, lip swelling, ocular hyperemia, decreased oxygen saturation, pain, pain in extremity, palmar erythema, erythematous rash, swollen tongue, tachycardia, tremor, and vomiting. Five patients had severe IARs.

^e Sampson’s criteria for anaphylaxis is the clinical criteria for the diagnosis of anaphylaxis from the 2006 National Institute of Allergy and Infectious Disease (NIAID).

The Applicant included six additional cases of IARs from LTS13769 with the December 2020 safety update.

The review team concluded the adverse events of hypersensitivity reactions, including anaphylaxis and IARs are known risks in the ERT and are not clinically different from those of alglucosidase alfa. These risks can be address in labeling and with routine pharmacovigilance. The review division will require the Applicant to include a boxed warning (BW) and listing in warnings and precautions for the risk of hypersensitivity reactions, anaphylaxis, and infusion-associated reactions, similar to Lumizyme, which were not initially included in the Applicant's proposed labeling.

5.2 IOPD PATIENTS (12 MONTHS AND YOUNGER)

As noted earlier, no safety data is available for patients 12 months of age or younger. The protocol criteria for ACT1432 excluded those that are treatment-naïve. In addition, patients with complete absence of GAA, classified as negative for cross-reactive immunologic material (CRIM), are likely to develop antibodies to ERT, making them resistant to treatment or have a higher risk for hypersensitivity reactions such as anaphylaxis and likely to require immune tolerizing therapies (ITT).¹⁵ In ACT14322, two patients were identified as CRIM-negative, which is insufficient for analysis. The review team concluded that avalglucosidsase alfa cannot be approved for children aged 12 months or younger due to lack of safety data and recommends a postmarketing commitment for a trial to demonstrate safety in this population.

6 Expected Postmarket Use

6.1 HEALTHCARE SETTING

A coordinated multidisciplinary approach is often employed in the management of patients with Pompe disease. Similar to Lumizyme, specialists in rare diseases, metabolic disorders, or biochemical geneticist are likely prescribers of avalglucosidase alfa. These prescribers are familiar with the risks associated with ERT for Pompe disease including hypersensitivity reactions, anaphylaxis, and infusion associated reactions. The majority of patients will receive their infusion from an outpatient setting such as an infusion centers or from a home infusion provider, although, some patients may receive the drug in a hospital setting. All of these healthcare settings and healthcare providers are required to be accredited, have policies and procedures in place, and are specially trained in the administration, monitoring, and treatment of adverse reactions associated with ERT.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for avalglucosidase alfa beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of avalglucosidase alfa in LOPD patients greater than 12 months of age for Pompe disease based on one efficacy trial (ETC14028) in addition to confirmatory evidence of efficacy and safety data. The review team determined the confirmatory evidence from published literature on the mechanism of action of avalglucosidase alfa, the natural history (i.e., well-known pathophysiology of Pompe disease), and the available data support the extrapolation of efficacy and safety data from pediatric IOPD and adult LOPD to pediatric LOPD are acceptable and justified in supporting avalglucosidase alfa's use in this population. (b) (4)

As there are no clinical trial data to support the dosing regimen of avalglucosidase alfa in patients < 16 years of age, a pharmacokinetic-based (PK) extrapolation is needed to justify the dosing regimen in the younger pediatric population. The Applicant conducted PK simulation studies, per the Agency's request, to determine appropriate dosing regimen across different age or body weight groups and to evaluate alternative dosing regimen in pediatric patients with lower body weight. The Applicant's simulation results indicated that smaller patients would need a higher dose to achieve comparable exposure to adult patients. An independent PK simulation conducted by the review team using virtual patients to compare the exposures at 40 mg/kg and 20 mg/kg across different body weight groups in the LOPD population suggested dosing regimen of 40 mg/kg for pediatric patients with lower body weights (e.g., < 30 kg) would provide similar or slightly higher exposure compared to adult patients receiving 20 mg/kg dosing regimen. Labeling discussions are on-going, but based on current findings, the review team recommends 40 mg/kg for pediatric patients weighing < 30 kg, and 20 mg/kg for patients weighing \geq 30 kg.

In patients who received avalglucosidase alfa in the clinical trials, AESIs of hypersensitivity occurred in 48% of patients with 5 patients meeting Sampson criteria for anaphylaxis, requiring interruptions in administration and or supportive therapy, and 30% experienced IARs. The majority of IARs were mild to moderate in severity. No deaths were attributed to avalglucosidase alfa. The adverse events associated with avalglucosidase are comparable to alglucosidase and the AESIs are well known risks in ERT which can be adequately addressed in labeling with a boxed warning and warnings and precaution statements and are consistent with Lumizyme labeling. Therefore, a REMS is not needed to ensure the benefits outweigh the risks of hypersensitivity reactions (including anaphylaxis) and IARs associated with avalglucosidase alfa for Pompe disease. There is a need for additional therapies for Pompe disease and avalglucosidase alfa's safety profile is comparable to already marketed ERT, such as Lumizyme. We expect avalglucosidase alfa will be limited to prescribers and healthcare providers who are familiar with Lumizyme and are knowledgeable on how to monitor and manage the risks such as hypersensitivity,

anaphylaxis, and IARs associated with this product. Further, the review division will require a pregnancy and lactation study post-approval, which was not available in the submission.

9 Conclusion & Recommendations

Based on the available data, we agree that a REMS is not necessary to ensure the benefits outweigh the risks for LOPD patients greater than one year old. The safety profile of Nexviazyme is comparable to Lumizyme. The safety concerns associated with Nexviazyme are known risks in the ERT class and include hypersensitivity reactions including anaphylaxis and infusion-associated reactions. We agree labeling, consisting of a BW and risk statements in Warnings and Precautions, is needed to convey the risks to prescribers and is consistent with Lumizyme labeling. Healthcare prescribers and healthcare settings that administer ERT for Pompe disease are familiar with these risks and are specially trained to monitor and manage adverse events associated with these products. Hospitals, infusion centers, and home infusion services are required to be accredited and have established policies and procedures for managing adverse reactions associated with ERT. The Applicant agreed to a PMC to evaluate the efficacy and safety in pediatric patients with IOPD, and to conduct PMRs in pregnancy and lactation to assess adverse effects, pregnancy outcomes, and concentration of avalglucosidase alfa in breast milk.

Should DRDMG have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 REFERENCES

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